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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/613,975
Filing Date: July 03, 2003
Appellant(s): WISE ET AL.

William C. Geary III (Reg. Number 31359)
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/20/2007 appealing from the Office action mailed 5/18/2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W.B. Saunders company (Philadelphia) in 1988.

Dorland's Medical Dictionary (29th Edition, 2000).

Stedman's Medical Dictionary (27th Edition, 2000).

Attwood, T. K. (Science Vol. 290,) October 20, 2000).

Pachuk, et al. Curt Opin Mol Ther. 2(2): 188-98 (April 2000).

Barnes, et al. Curr Opin Mol Ther. 2000 Feb; 2(1): 87-93 (February 2000).

Watts and Kennedy Int. J. Parasitol. 29(8): 1149-63 (1999).

O'Hagan Derek (Journal of Pharmacy and Pharmacology, Vol. 50, No. 1, pp.1-10, 1997).

McDonnel et al. (Medscape General Medicine, Vol.1, No 3, 1999).

US 6,689,608 Mikos et al. 02-2004

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

a) Claims 1, 3-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition (a mucoadhesive controlled released particulate delivery system) inducing immunogenic response against certain pathogens (Malaria and Anthrax), does not reasonably provide enablement for a vaccine for inducing immune response against all pathogens as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP) 2164.01(a). Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples (6) the quantity of experimentation, (7) the relative skill of those in the art, and (8) the breadth of the claims.

In the instant case claims 1, 3-11 are very broad and drawn to a vaccine. The only given example in the specification is in pages 11 and 14, mentioning the production of antigens for certain species of malaria and anthrax. When a compound or composition claim is limited by a particular use, enablement of that claim should be

evaluated base on that limitation. See in re Vaeck, 947 F. 2d 488, 495, 20 USPQ 2d 1438, 1444 (Fed Cir, 1991).

Dorland's Medical Dictionary (29th Edition, 2000) defines "vaccine" as "a suspension of attenuated or killed microorganisms (bacteria, viruses, or rickettsiae), or of antigenic proteins derived from them, administered for the **prevention, amelioration, or treatment of infectious diseases**. In the instant case the applicants' invention is not enabled for the **prevention, amelioration, or treatment of all infectious diseases**. And one skilled in the art will not be able to make/and or use the invention without undue experimentation commensurate in scope with the claims.

Stedman's Medical Dictionary (27th Edition, 2000) defines pathogen any virus, microorganism (i.e. bacteria, parasites and fungi) or other substance causing disease. The term pathogen is very broad and can include any organism or substance disease causing in humans, animals, plants, fish etc.

The term inducing immune response is also broad and include preventive immune response, as well induced and innate immune response. The claims are very broad and drawn to a vaccine, which encompasses any pathogen. The specification fails to teach a skilled artisan how to administer the claimed composition for immune protection. The specification presents a paper protocol in this regard. The specification has not taught a skilled artisan how to use the invention as presently claimed. Appellants have not shown or disclosed a correlation between in vitro and in vivo studies or that there are animal models that correlate to human (i.e. person) efficacy. Appellants' specification fails to provide guidance to the skilled artisan on the parameters for DNA vaccine for the breadth of the claimed invention. Numerous factors complicate the DNA vaccine therapy art, which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's

compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. Attwood, T. K. (Science Vol. 290,) October 20, 2000) teach that to predict genes in uncharacterized DNA is unreliable, it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences, and knowing the structure does not inherently tell us the function (see page 471). In the instant invention there is no correlation between structure and function. Additionally, the specification does not provide any working examples, which enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic (i.e. DNA) constructs of all pathogens, which would result in the desired effect (prevention and treating disease). Even assuming that an effective genetic material is constructed, it is not evident that DNA encode specific antigen to elicit immune response or to prevent disease. Therefore, even if the specification enabled the construction of the delivery vehicle comprising malaria DNA in mice, in the absence of particular guidance, the artisan would have been required to develop *in vivo* and *ex vivo* means of practicing the claimed methods and such development in the nascent and unpredictable DNA vaccine art would have been considered to have necessitated undue experimentation on the part of the practitioner.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention. For example Appellants" arguments on 01/08/2007 have been acknowledged. Appellants' in pages 7-9 argue:
The present application is directed to compositions, which provide controlled release of DNA vaccines. The claims define encapsulating nucleic acid encoding an antigen eliciting an immune response to a pathogen in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95%

void volume, or particles thereof DNA encoding antigen is encapsulated into a mucoadhesive controlled release particulate formulation to achieve sustained delivery of the vaccine and to maintain an immune response.

The specification clearly enables a skilled artisan to make and use the claimed vaccine formulation. The pathogens and antigens are known. The specification at least at page 11, lines .1-3 states that the antigen is a nuclei acid molecule encoding a protein that induces immunity. Suitable antigens are known and available from commercial, government and scientific sources (see the specification at least at page 11, lines 14-15). The claims are drawn to anew formulation providing a means for enhancing mucosal delivery of these nucleic acids encoding "known antigens. The claims are drawn to an improved DNA vaccine formulation generally, not a specific vaccine. Appellants do not claim to have invented DNA vaccines, and indeed have provided much evidence to show that DNA vaccines are known. The specification and application instead are drawn to the advantages obtained using the polymeric carrier. The best evidence against the examiner's rejection is the article cited by the Examiner in the Office Action mailed December 22, 2003, O'Hagan, J. Pharm. Pharmacol. 50:1-10 (1997) ("O'Hagan"), a copy of which is enclosed in the Appendix, dated four years before the priority date of this application. O'Hagan makes clear that even as of 1997, nucleic acid vaccines, while not being perfect and having some FDA issues, were effective and could be delivered using a polymeric carder. Additional papers were enclosed with the Amendment and Response filed August 10, 2004 to show that DNA vaccines are considered to be enabled and vaccination with them does not require "undue experimentation". See Pachuk, et al. Curt Opin Mol Ther. 2(2): 188-98 (April 2000); Barnes, et al. Curr Opin Mol Ther. 2000 Feb; 2(1): 87-93 (February 2000); and Watts and Kennedy Int. J. Parasitol. 29(8): 1149-63 (1999) ("Watts"), copies of which are enclosed in the Appendix. The Examiner pointed to Pachuk, page 188 wherein is stated that "DNA vaccine technology is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans as rebuttal to Appellants use of Pachuk as evidence that DNA vaccines are enabled. Appellants respectfully draw the Examiners attention to the fact that Pachuk is not stating that

research needs to be done for DNA vaccines to work, but to improve the efficiency with which they work which means that they do work. Also, the Examiner quoted from Pachuk at page 195, which states "it is recognized that one of the major limitations to the success of DNA vaccines is its delivery. This in fact is the problem the present application seeks to solve (see the specification at least from page 9, line 26until page 10, line 31). Also quoted by the Examiner was the sentence in Pachuk stating that 'it is unclear which cell are to be targeted for optimal eliciting of immune response" (referencing Pachuk, page 188). The specification discusses the cells to be targeted at least at page 10, lines 19-31.

The examiner has provided no evidence whatsoever that this method would not work; only unsupported allegation based on the belief that "the claims are very broad" (page 3, August 7, 2006, in a statement identical to the previous office action).

In response to appellants' arguments in regard to analysis of references cited by the office and applicants concerning scope of enablement rejections, the office will clarify for the record that the rejection is based on scope of enablement. The appellants'' are enabled for composition (a mucoadhesive controlled released particulate delivery system) inducing immunogenic response against certain pathogens (Malaria and Anthrax), does not reasonably provide enablement for a vaccine for inducing immune response against all pathogens as claimed. As mentioned above the claims specifically claim 1 is broadly drawn to any vaccine (i.e. prevention and treatment) for any pathogen (i.e. any virus, microorganism (i.e. bacteria, parasites and fungi) or other substance causing disease). In response to appellants'' arguments that the pathogens and antigens are known Ellis, R.W. (Chapter 29 of " VACCINES" [Plotkin, S.A. et al. (eds) published by W.B. Saunders company (Philadelphia) in 1988 recites that It is well recognized in the art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that " The key to the problem (of vaccine development) is the identification of protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... And thus protect the host against attack by the pathogen". In response to Pachuk, page 188 wherein is stated that "DNA vaccine

technology is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans and appellants' rebuttal use of Pachuk as evidence that DNA vaccines are enabled. The office brings appellants" attention to the fact that Pachuk is stating that research needs to be done for to improve the efficiency with which they work which means it is determined that it would require undue experimentation to make and use the Invention commensurate in scope with the claims.

b) Claims 1, 3-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recited the limitation" a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particle "It is not clear if the pathogen it self is encapsulated in the particle or it is the DNA encoding a specific antigen in encapsulated in the particle. It is also not clear if the DNA encoding the antigen from a pathogen.

c) Claims 1, 3-5 and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hagan Derek (Journal of Pharmacy and Pharmacology, Vol. 50, No. 1, pp.1-10, 1997). Prior art of record. USPTO 892, 12 /22/2003 in view of Mikos et al. (US 6,689,608 B1).

The claims are drawn a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen in a biodegradable polymer.

O'Hagan Derek teaches a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen in a biodegradable polymer (see abstract). O'Hagan teaches poly (lactide-co-glycolide) a biodegradable polymer (page 6). O'Hagan teaches a variety of pathogens including malaria and *Helicobacter pylori* (see pages 2 and 3). O'Hagan teaches encapsulation (page 6), adjuvants (page 5) particulates less than 5 micron and greater than 10 micron (see page 6). O'Hagan teaches mucosal immunization including nasal and oral (page 4).

O'Hagan does not specifically teach that the composition is mucoadhesive. However, O'Hagan teaches that mucosal administration of the vaccine, which enhances the effectiveness of the vaccine (see abstract). O'Hagan teaches all the limitations of claimed invention. Limitations such as mucoadhesiveness of the formulation will be an inherent property of a microparticle formulated for mucosal delivery. O'Hagan does not explicitly teach an opened –celled polymeric foam of approximately 95% void volume or a particle thereof.

Mikos et al. teach a polymeric matrix formed of poly (lactide-co-glycolide) a biodegradable polymer with a polymeric foam of approximately 95% void volume (see abstract, claims specially claim 1 and column 4).

It would have been *prima facie obvious* to one of ordinary skill in the art at the time the invention was made to combine the teachings of O'Hagan with the teachings of T Mikos et al. to obtain a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particle a mucoadhesive controlled release particle comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof .

One of skilled in the art would have been motivated to use polymer of 95% void volume taught by Mikos et al. replacing biodegradable polymer to deliver immunogenic compositions. One of ordinary skill in the art would have been motivated by the teachings of O'Hagan that in delivery of antigens by biodegradable polymers including PLG the particle size shown to be an important factor affecting immunigenicity (see O'Hagan page 6).

(10) Response to Argument

a) Appellants' arguments on a notice appeal submitted 8/20/2007 have been acknowledged. Appellants' argue:

- Claims 1, 5, and 8 are enabled. The claims define compositions providing controlled release of DNA vaccines. The claims require encapsulation of nucleic acid encoding an antigen eliciting an immune response to a pathogen in a

mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof. DNA encoding antigen is encapsulated into a mucoadhesive controlled release particulate formulation to achieve sustained delivery of the vaccine and to maintain an immune response.

- In response, the Examiner cited to Ellis, *"New Technologies for Making Vaccines"* in Vaccines, Plotkin S.A., et at (eds), WB Sanders Company (Philadelphia) (1988) pp 568-67t ("Ellis") as evidence, that it is well recognized in the art that it is unclear whether antigens derived from a pathogen will elicit immunity, specifically citing to Ellis, page 571, 2nd full paragraph, where it is stated that "the key problem of vaccine development is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.., and thus protect the host against attack by the pathogen". Ellis does not refute Appellants' statement that pathogens and antigens are known in the art. Appellants agree with the statement in Ellis, that the component of the pathogen that can elicit immune response has to be identified; this does not mean that such components have not been identified. In fact, Ellis goes on to discuss successful use of DNA technology to develop vaccines for humans (See Ellis, page 571, from left col. 3rd paragraph to right col. 2nd paragraph). The specification at least at page 11, lines 1-3 states that the antigen is a nucleic acid molecule encoding a protein that induces immunity. Suitable antigens are known and available from commercial, government, and scientific sources (see the specification at least at page 11, lines 14-15).

- With respect to the statement on page 3 that the pathogen can be any substance causing disease, that is not correct. The claim language must be interpreted in view of the specification and the claim per se. The claims require that the pathogen must have DNA that encodes an antigen that elicits immunity against the pathogen. It is very clear beginning at page 1 that pathogen is an infectious agent, such as a bacteria or virus. Note in particular at page 7, lines 9-12, which

states in relevant part "It is therefore an object of the present invention to provide a method and compositions to provide prolonged, improved protection against infectious pathogens, including *P. falciparum, F. Tularensis, H. pylori, and 17. anthracis,* especially using oral or intranasal routes of administration. Moreover, the specification refers to more than just malaria (pages 23-32) and anthrax (pages 33-34). See page 13, for specific tularemia antigens. Reference to an HIV vaccine and DNA plasmid vector is found at pages 23-24, along with the description of how to make the vector.

- Other pathogens are described in detail in the background of the invention. The claims are drawn to a new formulation providing a means for enhancing mucosal delivery of these nucleic acids encoding known antigens. The claims define an improved DNA vaccine formulation generally, not a specific vaccine. Appellants do not claim to have invented DNA vaccines, and indeed have provided much evidence to show that DNA vaccines were known as of the date the application was filed. See, for example, Partidos, et al. J. *Immunol. Method.* t95:135-138 (1996); Pertmer, et al., *Vaccine* 13(15):1427-1430 (1995); Singh, et al., *Pharm. Res.* 8(7):958-961 (1991); Smith, et al., *Oral Microbiol. Immunol.* 15:124-130 (2000); and Thomasin, et al., J. *Control. Rel.* 41:131-145 (1996) (all cited at page 21 of the specification and in the Information Disclosure Statement made of record June 14, 2004). The specification and application instead are drawn to the advantages obtained using the polymeric carrier.

- The Examiner further cited to a summary by McDonnel, et al., Medscape General Medicine, (3) (1999) ("McDonnel"), which states many prophetic problems that could arise with DNA vaccines. According to McDonnel and cited by the Examiner, there is no evidence of these problems having occurred *(See* the office action mailed on May 18, 2007, page 5). It is therefore unclear how McDonnel is evidence that DNA vaccines do not work or are unpredictable. Recitation of potential problems is not evidence of unpredictability.

- Claim 3 is enabled. Mucoadhesives are known in the art, and the specification discloses the addition of a mucoadhesive at least at pages 21-23. The specification exemplifies improved mucoadhesion observed with particles with a mucoadhesive as an added component *(See* the specification from page 22, line 1 until page 23, line 2). The examiner has provided no basis for alleging one would not know how to make a mucoadhesive formulation. Therefore, claim 3 is enabled.

- Claim 4 is enabled. Enteric coatings are routinely used in the pharmaceutical art, can be purchased commercially, and the specification at least at page 23, lines 9-14 provides an example of an enteric coating. It would therefore be routine for a skilled artisan to make a vaccine as defined by claim 1 including an enteric outer coating or capsule as required by claim 4. Therefore, claim 4 is enabled.

- Claims 6 and 7 as defined by claims 6 and 7, the composition can be formed by a method that contains the following steps: (1) lyophilizing a solution of a biodegradable polymer to form an open- celled polymeric foam of approximately 95% void volume, (2) impregnating the foam with an aqueous solution of the nucleic acid, (3) lyophilizing the foam to remove the water, and (4) extruding the resulting matrix at ultrahigh pressures as defined by claim 6 (disclosed least at pages 27-28). Again, the examiner has provided no basis for rejecting this claim other than the allegation that because the claims are "very broad" they must not be enabled. The specification discloses administration of the vaccines at least at page 32. The specification at least at page 26 describes appropriate size ranges for the particles as defined by claims 5 and 8. Methods for encapsulating nucleic acids into the polymeric foam are disclosed in the specification on page 19. Therefore the specification not only describes how to make and use the claimed formulation, but demonstrates that appellants have actually made and used the formulation.

- Claim 9 is enabled. The specification from page 1, line 23 to page 6, line 7 discusses in detail malaria, tularemia, and anthrax, diseases which are caused by *Plasmodium falciparum, Francissla tularensis,* and *Bacillus anthracis,* respectively. Antigens to these pathogens are known in the art (see the specification from page 11 to page 17, discussing antigens to the four pathogens listed in claim 9). It would be routine for a skilled artisan to make a nuclei acid molecule encoding antigens to these pathogens and encapsulate them in a mucoadhesive controlled release formulation, based on the teachings in the specification, for the manufacture of a vaccine
formulation for inducing an immune response to the pathogens listed in claim 9. The examiner has already acknowledged that the specification is enabling for two of these three specific pathogens. Therefore, claim 9 is enabled.

- Claim 10 is enabled. Adjuvants are known in the art, and the specification at least at page at page t 1, lines t 7- 24 provides examples. It would therefore be routine for a skilled artisan to make a vaccine as defined by claim 1 including adjuvants as required by claim 10, as described in the specification, for the reasons discussed above. Therefore, claim 10 is enabled.

- Claim 11 is enabled. Methods for measuring DNA release are known in the art, and are disclosed in the specification at least from page 29, line t8, to page 31, line 28. The specification at least from page 23, line 19, to page 24, line t6, provides an example showing recovery of DNA from PLGA matrices throughout a 6 week incubation period. The examiner has provided no reason why one skilled in the art would not be able to measure DNA release, nor that the formulation of claim 1 would release DNA. Therefore, claim 11 is enabled.

In response to appellants' arguments in regard to analysis of references cited by the office and appellants' concerning scope of enablement rejections, the office will clarify for the record that the rejection is based on **scope of enablement**. The appellants' are enabled for composition (a mucoadhesive controlled released particulate delivery

system) inducing immunogenic response against certain pathogens (Malaria and Anthrax), does not reasonably provide enablement for a vaccine for inducing immune response against all pathogens as claimed. As mentioned above the claims specifically **claim 1 is broadly drawn to any vaccine** (i.e. prevention and treatment) **for any pathogen** (i.e. any virus, microorganism (i.e. bacteria, parasites and fungi) or other substance causing disease). In response to appellants' arguments that the pathogens and antigens are known Ellis, R.W. (Chapter 29 of " VACCINES" [Plotkin, S.A. et al. (eds) published by W.B. Saunders company (Philadelphia) in 1988 recites that It is well recognized in the art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that " The key to the problem (of vaccine development) is the identification of protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... And thus protect the host against attack by the pathogen". In response to Pachuk, page 188 wherein is stated that "DNA vaccine technology is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans and appellants' rebuttal use of Pachuk as evidence that DNA vaccines are enabled. The office brings appellants' attention to the fact that Pachuk is stating that research needs to be done for to improve the efficiency with which they work which means it is determined that it would require undue experimentation to make and use the Invention commensurate in scope with the claims.

Appellants' arguments have been fully considered but they are not persuasive because the specification, while being enabling for a composition inducing immune response against certain pathogens, does not reasonably provide enablement for a vaccine for inducing immune response against all pathogens. The claims are very broad and drawn to a vaccine, which encompasses any pathogen. The specification fails to teach a skilled artisan how to administer the claimed composition for immune protection. The specification presents a paper protocol in this regard. The specification has not taught a skilled artisan how to use the invention as presently claimed.

Appellants have not shown or disclosed a correlation between in vitro and in vivo studies or that there are animal models that correlate to human (i.e. person) efficacy. Appellants' specification fails to provide guidance to the skilled artisan on the parameters for DNA vaccine for the breadth of the claimed invention. Numerous factors complicate the DNA vaccine therapy art, which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated. Additionally, the specification does not provide any working examples, which enable the claimed invention. Nor does the specification provide any guidance to the skilled artisan on how to make and use genetic constructs of all pathogens, which would result in the desired effect. Even assuming that an effective genetic material is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefit. Therefore, even if the specification enabled the construction of the gene delivery vehicle comprising a cell targeting element, in the absence of particular guidance, the artisan would have been required to develop *in vivo* and *ex vivo* means of practicing the claimed methods and such development in the nascent and unpredictable gene therapy art would have been considered to have necessitated undue experimentation on the part of the practitioner. A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques

where necessary, as to enable those persons skilled in the art to make and utilize the invention.

b) Appellants' arguments on a notice appeal submitted 8/20/2007 have been acknowledged. Appellants' argue:

- Claims 1 and 3-11 are non-obvious over O'Hagan in view of Mikos. Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.,* 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR int'l Co. v. Teleflex, Inc.,* 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining O'Hagan is a review article discussing the advances in vaccine adjuvants for systemic and mucosal *administration prior to 1997.* It should be noted that O'Hagan is cited above by Appellants to support enablement of their claims, since O'Hagan describes vaccines, including vaccines made by recombinant DNA technology and nucleic acid based vaccine, as being known and effective no later than 1997, five years before the priority date of this application. O'Hagan discloses the use of biodegradable polymers as vaccine adjuvants, in particular, the encapsulation of protein antigens into poly (lactide-co-glycolides) microparticles and the use of emulsions formed of materials such as mineral oil, and those which are advantageous for mucosal administration.
- Mikos discloses polymeric materials used to make a pliable, non-toxic, injectable porous template for vascular ingrowth. The materials disclosed in Mikos are used for tissue engineering and regeneration (Mikos, abstract); not nucleic acid delivery or indeed, vaccine delivery. Even if one combined O'Hagan with Mikos, one would still not have a vaccine delivery formulation, much less one as

claimed. *Claims 1, 5, and 10 are non-obvious over 0 'Hagan in view of Mikos* O'Hagan does not disclose the claimed composition. Mikos does not make up for this deficiency. While O'Hagan states that delivery of a vaccine composition by mucosal administration would be "ideal" (Table I, p. 2), the reference does not teach or suggest enhancing antigenicity by increasing mucoadhesion using a porous polymeric matrix or particles thereof.

- The Examiner acknowledge that O'Hagan does not disclose or suggest a composition comprising nucleic acid encoding an antigen that is encapsulated in a mucoadhesive controlled release particulate formulation. However, the Examiner alleges that O'Hagan discloses mucosal immunization including nasal and oral (citing O'Hagan, page 4), and that mucoadhesiveness of the formulation will be an inherent property of a microparticle formulated for mucosal delivery. The Examiner has no basis for such a conclusion of inherency. According to the MPEP §2112(IV), *"In* relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Exparte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)". The Examiner has not done so. It appears as though the Examiner is stating that just because a composition is intended for mucosal delivery it would automatically have mucoadhesive properties. This in fact is not the case. The specification at least at page 22, lines 21-25 demonstrates little or no adherence to the dome region of murine intestinal loops, of particles consisting of PLGA, with no bioadhesive. There is no disclosure in the prior art of the need for a high void volume within the matrix. No art has been cited as showing this claimed element. Thus, a combination of O'Hagan and Mikos does not recite all of the limitations of the claims as required by a rejection under 35 U.S.C. 103(a). O'Hagan does not disclose a vaccine composition comprising a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void

volume or particles thereof. The Examiner acknowledged this, but provided Mikos to make up for this deficiency. Mikos discloses the use of semicrystatline polymers such as poly (lactic acid-glycolic acid) having a porosity in the range of 50-95% for use in tissue regeneration, which allows vascular ingrowth and the introduction of cells into the matrix without damage to the cells or patient. This is not a drug delivery device, much less one for delivery of nucleic acid. There is no motivation for one of ordinary skill in the art to combine Mikos with O'Hagan as the Examiner has done. The Examiner is not only using impermissible hindsight reconstruction, the Examiner is also not considering the references as a whole *(See* MPEP §2141.02). The legal standard makes it quite clear that it is not sufficient to use that which applicants' claim as a starting point, then searching through the prior art, picking and choosing to find those features that may be known. The art must lead one of skill to it, i.e., the motivation to combine as applicants have done, with a reasonable expectation of success, must be found in the cited art.

- According to the Examiner, one of ordinary skill in the art would have been motivated to replace the biodegradable polymer in O'Hagan with the polymer of 95% void volume taught by Mikos, because O'Hagan discloses that in delivery of antigens by biodegradable polymers including PLG, the particle size is shown to be an important factor affecting immunogenicity (citing O'Hagan, page 6). It is unclear how such a disclosure by O'Hagan would motivate one of ordinary skill in the art to combine O'Hagan and Mikos to arrive at the claimed composition, which does not recite particle size, and particularly as it was cited as it relates to void volume. There is simply no disclosure of why one needs mucoadhesion and a very high void volume matrix to be used for delivery of nucleic acid vaccines. The Examiner has provided no reason why one of ordinary skill in the art would combine O'Hagan and Mikos to arrive at the claimed composition. The Examiner has focused his analysis on the obviousness of the differences of the claimed composition with the prior art, instead of on the obviousness of the claimed

composition as a whole. Not only does the prior art either alone or in combination recite all of the limitations of the claims, there would be no motivation for one of ordinary skill in the art to combine Mikos and O'Hagan as the Examiner has done. Therefore, claims 1, 5, and 10 are non-obvious over O'Hagan in view of Mikos.

- Claim 3 is non-obvious over *0 'Hagan in view of Mikos* Claim 3 requires that the composition of claim 1 further comprise a mucoadhesive polymer coating. As previously discussed, O'Hagan does not disclose the encapsulation of DNA n a mucoadhesive controlled release particulate formulation, nor that the composition further comprise a mucoadhesive. Mikos does not disclose a formulation comprising an open-celled foam for encapsulating nucleic acid, which further comprises a mucoadhesive polymer coating. No art has been cited as disclosing PLGA as a mucoadhesive polymer. Thus the prior art in combination neither recites all of the limitations of the claims as required by a rejection under 35 U.S.C. §103(a), nor suggests a desirability of the combination as the Examiner has done. Therefore, claim 3 non-obvious over O'Hagan in view of Mikos. *Claim 4 is non-obvious over O'Hagan in view of Mikos* Claim 4 requires the composition of claim I further comprise an enteric outer coating or capsule. O'Hagan does not disclose or suggest a composition for inducing an immune response to a pathogen, that comprises an open-celled polymeric foam of approximately 95% void volume or particles thereof, and further comprises an enteric outer coating or capsule as recited in claim 4. Mikos does make up for this deficiency. Thus the prior art in combination neither recites all of the limitations of the claims as required by a rejection under 35 U.S.C. § 103 (a), nor suggests a desirability of the combination as the Examiner has done. Therefore, claim 4 is novel over O'Hagan and Perez. Claim 9 is non-obvious over *O'Hagan in view of Mikos* Claim 9 recites all of the limitations of claim 1 and requires that the pathogen be *Plasmodium falciparum, Francisella tularensis, Bacillus anthracis* and *Helicobacter pylori.* For discussed with respect to claims 1, 5, and 8, O'Hagan

does not disclose a composition for inducing an immune response to any of the pathogens listed in claim 9. Mikos does not make up for this deficiency. Therefore, claim 9 non-obvious over O'Hagan in view of Mikos. Claim 11 None of O'Hagan or Mikos, alone or in combination, disclose or suggest release of antigen over a period of weeks to months from an open celled foam. Accordingly, claim 11 is non-obvious over O'Hagan in view of Mikos.

- In Summary Claims 1 and 3-11 are non-obvious over the cited art, O'Hagan and Mikos, since neither O'Hagan nor Mikos, either alone or in combination, disclose each and every claimed limitation.
  Moreover, even if the references in combination disclosed each claimed limitation, there is no motivation to modify and combine as appellants have done, with a reasonable expectation of success in long-term release of antigen.

In response to appellants' arguments it is this office's position that under the TSM test, a claimed invention is obvious when there is a teaching, suggestion or motivation to combine prior art teachings. The teaching, suggestion or motivation may be found in the prior art, in the nature of the problem, or in the knowledge of a person having ordinary skill in the art. According to supreme court on KSR International Co. v. Teleflex Inc. 82 USPQ2d 1385, 1396 (2007), the TSM test is one of a number of valid rationales that could be used to determine obviousness. It is not the only rationale that maybe relied upon to support a conclusion of obviousness.

In the present case it would have been *prima facie obvious* to one of ordinary skill in the art at the time the invention was made to combine the teachings of O'Hagan with the teachings of T Mikos et al. to obtain a vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particle a mucoadhesive controlled release particle comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof .

One of skilled in the art would have been motivated to use polymer of 95% void volume taught by Mikos et al. replacing biodegradable polymer to deliver immunogenic compositions. One of ordinary skill in the art would have been motivated by the teachings of O'Hagan that in delivery of antigens by biodegradable polymers including PLG the particle size shown to be an important factor affecting immunigenicity (see O'Hagan page 6).

It should be also noted that KSR forecloses the argument that a **specific teaching**, suggestion or motivation is required to support a finding of obvoiuness. See the recent Board decision *Ex parte Smith*--USPQ2d--, June 25, 2007. In response to appellants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

c) Claims 1 and 3-11 were rejected under 35 U.S.C. §112 second paragraph as allegedly being unclear. According to the Examiner, claim 1 recites the limitation % vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particle", and it is unclear if the pathogen itself is encapsulated in the particle or it is the DNA encoding a specific antigen encapsulated in the particle. Claim 1 is drawn to:

A vaccine composition for inducing an immune response to a pathogen comprising a nucleic acid encoding an antigen eliciting an immune response to the pathogen encapsulated in a mucoadhesive controlled release particulate formulation comprising an open-celled polymeric foam of approximately 95% void volume, or particles thereof. Appellants respectfully submit that one of ordinary skill in the art would understand that the nucleic acid, not the pathogen, is encapsulated into the particle. A claim is interpreted in light of the specification (See MPEP §2111) as well as based on how one of ordinary skill in the art would understand the ordinary language of the claims. It would

be clear to one of ordinary skill in the art that the claims do not require using pathogens, dead or alive in the claimed compositions, from the disclosure in the specification. Therefore, claims 1 and 3-11 are clear.

In response to appellants' arguments it is this office's position that claim language is confusing it is unclear if the pathogen itself is encapsulated in the particle or it is the DNA encoding a specific antigen encapsulated in the particle.

Respectfully submitted,

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